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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/617,978	07/11/2003	Rafael Herrmann	035718/260673	4095

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EXAMINER	
KUBELIK, ANNE R	
ART UNIT	**PAPER NUMBER**
1638	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/617,978	HERRMANN ET AL.	
	Examiner	Art Unit	
	Anne R. Kubelik	1638	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 July 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7,13-19,21-26,30,31,38,40 and 42* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7,13-19,21-26,30,31,38,40 and 42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-7, 13-19, 21-26, 30-31, 38, 40 and 42 are pending.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 112

3. Claims 1-7, 13-19, 21-26, 30-31, 38, 40 and 42 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The rejection is repeated for the reasons of record as set forth in the Office action mailed 14 May 2007. Applicant's arguments filed 19 July 2007 have been fully considered but they are not persuasive.

The claims are drawn to pesticide-encoding nucleic acids with 95% identity to bases 73-249 or SEQ ID NO:17 or bases 64-240 of SEQ ID NO:14.

Nucleic acids with 95% identity to the recited 177 bases of SEQ ID NO:17 or SEQ ID NO:14 would have 8 nucleotide substitutions relative to bases 73-249 or SEQ ID NO:17 or bases 64-240 of SEQ ID NO:14. These nucleic acids thus encompass those that encode proteins with 8 amino acid substitutions relative to the 58 amino acid long SEQ ID NO:20; these proteins would have 86% identity to SEQ ID NO:20.

The claimed nucleic acids encode proteins with any type of substitution, insertion or deletion relative to SEQ ID NO:20.

The specification does not describe the relevant characteristics or motifs of the claimed nucleic acids.

The claimed function of nucleic acids with 95% identity to bases 73-249 or SEQ ID NO:17 or bases 64-240 of SEQ ID NO:14 is that the encoded proteins be pesticidal. The pesticidal function is not specific; even the specification lists 4 pages of different pests (pg 50-53).

The structural features that distinguish pesticidal proteins with 86% identity to SEQ ID NO:20 from other proteins with 86% identity to SEQ ID NO:20 are not described in the specification. The structural features that associate structure with activity against a specific pest are not described. The necessary and sufficient structural elements of a protein with pesticidal activity are not described.

All of the claimed nucleic acids are novel, and thus the prior art cannot provide no well-developed field of prior art to describe the full scope of claimed nucleic acids. However, Zeng et al (2006, Peptides 27:1745-1754) teach that the four proteins most closely related to SEQ ID NO:20, are toxic or lethal to mice (pg 1749, left column).

The only species described in the specification are bases 73-249 or SEQ ID NO:17 or bases 64-240 of SEQ ID NO:14, both of which encode SEQ ID NO:20.

Since the disclosure fails to describe the common attributes that identify members of the genus, and because the genus is highly variant, bases 73-249 or SEQ ID NO:17 or bases 64-240 of SEQ ID NO:14 alone are insufficient to describe the claimed genus.

Hence, Applicant has not, in fact, described pesticide-encoding nucleic acids with 95% identity to bases 73-249 or SEQ ID NO:17 or bases 64-240 of SEQ ID NO:14. Because the

sequences are not described, the method of using the sequences to alter a plant pest resistance is likewise not described, and the specification fails to provide an adequate written description of the claimed invention.

Therefore, given the lack of written description in the specification with regard to the structural and functional characteristics of the compositions used in the claimed methods, it is not clear that Applicant was in possession of the claimed genus at the time this application was filed.

Applicant urges that the Federal Circuit made it clear that the Written description requirement requires that knowledge and level of skill in the art permit one to immediately envision the claimed product (response pg 3).

This is not found persuasive. Given that the four proteins most closely related to SEQ ID NO:20 are toxic or lethal to mice (Zeng et al, pg 1749, left column), one of skill in the art would not be able to immediately envision the claimed product based on the description in the specification.

Applicant urges that the Written Description Guidelines and *Lilly* state that written description requires a precise definition by structure, which is present in the 95% identity recitation (response pg 3-4).

This is not found persuasive. *Enzo* states: "the written description requirement would be met ... if the functional characteristics of [a genus of polypeptides] were coupled with a disclosed correlation between that function and a structure that is sufficiently known or disclosed" (emphasis added). The correlation between that function and a structure is not

sufficiently known in birtoxin-related proteins as a whole, and the description and assays provided in the specification are insufficient to describe this relationship.

Only a portion of the structural features have been described - the percent identity to SEQ ID NO:14 or 17. But because this includes nucleic acids in which the protein sequence has a large number of amino acid substitutions, those amino acid substitutions that do not alter the function of the protein must be described. They are not.

Applicant urges that all the claims recite a functional and structural limitation, and assays are taught and known in the art (response pg 4).

This is not found persuasive. The structural features that distinguish pesticidal proteins with 86% identity to SEQ ID NO:20 from other proteins with 86% identity to SEQ ID NO:20 are not described in the specification. The four proteins most closely related to SEQ ID NO:20 are toxic or lethal to mice (Zeng et al, pg 1749, left column). This is especially important, given that the goal of the instant invention is to find insect control strategies that are "benign to non-target populations" like animals and humans (specification, pg 1, lines 13-17).

Applicant urges that the terms "pesticidal activity" and "pesticidal polypeptides" are specific and defined in the specification (response pg 4-5).

This is not found persuasive because the functional description is very broad and encompasses a wide arrange of activities and a wide range of pests.

Applicant urges literal support for the claimed invention is not required (response pg 5).

This is not found persuasive because the specification does not describe the sequence of even one nucleic acid encoding a pesticidal protein with 8 amino acid substitutions relative to SEQ ID NO:20. Thus, Applicant was not in possession of the full scope of the genus as claimed.

Applicant urges that the specification describes SEQ ID NOs: 17 and 14, which are a representative embodiment of the claimed sequences, and sequences that fall within the scope of the claims can be identified by the methods in the specification (response pg 5).

This is not found persuasive. Both SEQ ID NO:14 and 17 encode SEQ ID NO:20. No nucleic acids that encode a pesticidal protein with 8 amino acid substitutions relative to SEQ ID NO:20 are described. Thus, Applicant was not in possession of the full scope of the genus as claimed.

4. Claims 1-7, 13-19, 21-26, 30-31, 38, 40 and 42 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for nucleic acids encoding proteins with 95% identity to SEQ ID NO:20, expression cassettes, host cells, and viruses comprising them, and methods of using them to alter plant pest resistance, does not reasonably provide enablement for pesticide-encoding nucleic acids with 95% identity to bases 73-249 of SEQ ID NO:17 or bases 64-240 of SEQ ID NO:14, expression cassettes, host cells, viruses, plants and seeds comprising them, and methods of using them to alter plant pest resistance. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. The rejection is repeated for the reasons of record as set forth in the Office action mailed 14 May 2007. Applicant's arguments filed 19 July 2007 have been fully considered but they are not persuasive.

The claims are broadly drawn to nucleic acids encoding pesticidal proteins with 95% identity to SEQ ID NO:20 and to pesticide-encoding nucleic acids with 95% identity to bases 73-

249 or SEQ ID NO:17 or bases 64-240 of SEQ ID NO:14. The claims are also drawn to expression cassettes, host cells, viruses, vectors, and plants comprising the nucleic acids, and methods of making the plants.

The instant specification, however, only provides guidance for isolation of proteins from arthropod venom and sequencing of the proteins (examples 1-4), southern corn rootworm and homopteran feeding assays (examples 5-6), construction of baculoviruses and expression of the proteins in insect cells (examples 7-8), construction of plant expression vectors encoding the pesticidal protein operably linked to a secretion signal sequence (examples 9-12), identification of cDNAs encoding neurotoxins from Centruroides vittatus and construction of vectors encoding them (examples 13-14); general guidance for transformation of rice, maize, soybean and assay of the plants for insect resistance (examples 15-20). SEQ ID NO:20 is Aam1 from Androctonus amoreuxi; SEQ ID NO:14 is a nucleic acid encoding it that uses rice-preferred codons and the sweet potato sporamin signal sequence, while SEQ IDNO:17 is optimized for expression in Stretomyces coelicolor and has the BAA signal peptide (paragraph spanning pg 11-12).

The instant specification fails to provide guidance for how to make pesticide-encoding nucleic acids with 95% identity to bases 73-249 or SEQ ID NO:17 or bases 64-240 of SEQ ID NO:14.

Nucleic acids with 95% identity to the recited 177 bases of SEQ ID NO:17 or SEQ ID NO:14 would have 8 nucleotide substitutions relative to bases 73-249 or SEQ ID NO:17 or bases 64-240 of SEQ ID NO:14. These nucleic acids thus encompass those that encode proteins with 8 amino acid substitutions relative to the 58 amino acid long SEQ ID NO:20; these proteins would have 86% identity to SEQ ID NO:20.

The guidance in the specification with respect to making amino acid substitutions in the proteins produced by the claimed nucleic acids is as follows:

The specification teaches making amino acid substitutions, deletions, truncations and insertions by methods including DNA shuffling and mutations, and suggests that conservative substitutions may be preferable, but are not required (pg 18, line 6, to pg 19, line 28).

Thus, from the guidance in the specification, it would appear that the vast majority of the amino acids in SEQ ID NO:20 could be substituted with any other amino acid.

SEQ ID NO:20 has 63-66% identity to four scorpion proteins, birtoxin, bestoxin, ikitoxin and dortoxin, taught by Hammock et al (WO 2003/028666, see search results), and these proteins have an even higher degree of relatedness if conservative amino acid substitutions are taken in account.

Zeng et al (2006, Peptides 27:1745-1754) teach that although the proteins have very similar structures, they have very different functions; birtoxin and dortoxin are lethal to mice, and bestoxin causes writhing in mice (pg 1749, left column).

SEQ ID NO:20 is much less related to other insect toxins of this protein class than to the mammalian toxins; for example, it only has 43-45% identity to four taught by Herrman et al (WO 2000/078957; see search results).

Thus, SEQ ID NO:20 may be a mammalian toxin, in which case, it would be unclear how one would use a plant transformed with a nucleic acid encoding it.

Further, even if SEQ ID NO:20 were not toxic to mammals, one of skill in the art would not know which 8 amino acid substitutions to make in SEQ ID NO:20 and still produce proteins

that are toxic to insects but not mammals, and the closest proteins to which to make comparisons are mammalian toxins.

The instant specification fails to provide guidance for which amino acids of SEQ ID NO:20 can be altered and to which other amino acids, and which amino acids must not be changed, to maintain pesticidal but not mammalicidal activity of the encoded protein. The specification also fails to provide guidance for which amino acids can be deleted and which regions of the protein can tolerate insertions and still produce a functional enzyme.

Further, making each additional mutation in a protein has an negative effect on the success of the outcome. Guo et al (2004, Proc. Natl. Acad. Sci. USA 101: 9205-9210) teach that while proteins are fairly tolerant to mutations resulting in single amino acid changes, increasing the number of substitutions additively increases the probability that the protein will be inactivated (pg 9209, right column, paragraph 2). Thus, making and analyzing proteins with 8 amino acid substitutions that also have pesticidal activity would require undue experimentation.

Thus, extensive teachings are required for making nucleic acids encoding pesticidal proteins with 8 amino acid substitutions relative to SEQ ID NO:20, as encompassed by the claimed nucleic acids. These teachings are not provided for by the specification. The specification also fails to overcome the unpredictability of making large numbers of amino acid substitutions in SEQ ID NO:20 as it provides no working examples of proteins with 8 amino acid substitutions relative to SEQ ID NO:20.

Given the claim breath, unpredictability, and lack of guidance as discussed above, undue experimentation would have been required by one skilled in the art to develop and evaluate

pesticide-encoding nucleic acids with 95% identity to bases 73-249 or SEQ ID NO:17 or bases 64-240 of SEQ ID NO:14.

Given the claim breath, unpredictability in the art, undue experimentation, and lack of guidance in the specification as discussed above, the instant invention is not enabled throughout the full scope of the claims.

Applicant urges that they need not demonstrate every nucleic acids encompassed by the claims, only that any experimentation not be undue (response pg 6).

This is not found persuasive because teach how to make and use nucleic acids within the full scope of the claims. Given the complex relationship between structure and function in birtoxin-related proteins (See Zeng et al, pg 1749, left column), and given that SEQ ID NO:20 is more closely related to mammalian toxins than to insect toxins, making toxins that are insect toxins and not mammal toxins requires more guidance than is given in the specification. Applicant is reminded that the specification does not teach how to use a plant transformed with a mammalian toxin.

Applicant urges that *Wands* does not require a working example of every nucleic acid encompassed by the claims (response pg 6-7).

This is not found persuasive. A working example of every nucleic acid encompassed by the claims is not being required. What is required is guidance for how to make the full scope of the claimed nucleic acids. The relatedness of SEQ ID NO:20 to insect toxins makes this unpredictable, and the specification fails to overcome this unpredictability by providing sufficient guidance.

Applicant urges that sequences that fall within the scope of the claims, guidance for making alterations, methods for assaying, guidance for determining percent identity and specific mutations that fall within the scope of the claims; *Wands* indicates that these should be afforded significant weight (response pg 7-8).

This is not found persuasive because the guidance is insufficient, given the scope of the claims and the potential mammalian toxicity of the proteins. Limiting the percent identity of the claimed nucleic acid and requiring a function do not teach which amino acid substitutions may be made in the proteins. Pg 18 merely suggests that conservative substitutions may be preferable, but are not required. The guidance on pg 23-28 merely discusses fragment size, percent identity, and calculation of percent identity. However, guidance for determining percent identity does not teach which amino acid substitutions are permissible. The guidance fails to sufficiently teach which 8 amino acid substitutions to make in SEQ ID NO:20, given the unpredictability in making amino acid substitutions in birtoxin-related proteins. The specification's lack of guidance as to which amino acids can be substituted and still retain pestical function without adding mammalian toxicity (if SEQ ID NO:20 isn't already a mammalian toxin), making the claimed nucleic acids would require undue experimentation.

Applicant urges that the highly divergent biological activities referred to by Zeng et al are not highly divergent, and at best teaches that administration to mice affects their activity in mice; as the instant claims are directed to pesticidal activity toward insect pests it is unclear how this makes making amino acid substitutions unpredictable (response pg 8).

This is not found persuasive. It is important that plants not be toxic to animals, of which mice are common human substitutes in toxicity tests. The instant specification even states (pg 1, lines 13-17):

> [C]hemical agents are under continuous scrutiny due to the potential for environmental contamination, selection of resistant populations of agronomic pests, and toxicity to non-target organisms such as beneficial insects, aquatic organisms, animals and humans. As a result, **alternative strategies for insect control are being sought that are** effective and yet **benign to non-target populations** and the environment. [emphasis added]

Given that SEQ ID NO:20 is more closely related to mammalian toxins than to insect toxins and the specification's lack of guidance as to which amino acids can be substituted and still retain pesticidal function without adding mammalian toxicity (if SEQ ID NO:20 isn't already a mammalian toxin), much more than the general guidance that is given in the specification is required.

Applicant urges that Guo et al, Lazar et al and Hill et al continue to be cited and mischaracterized; Lazar et al and Hill et al teach alterations of highly conserved amino acids will disrupt function and Guo et al teach quantizing a protein's tolerance to random changes (response pg 8-9).

This is not found persuasive. Given the lack of guidance in the specification, one of skill in the art would need to make random changes, which Guo et al teaches has a high probability of leading to protein inactivation. Additionally, even if the protein is not inactivated, SEQ ID NO:20's being more closely related to mammalian toxins than to insect toxins makes making proteins that are toxic to insects and not humans unpredictable.

Applicant urges that making the claimed nucleic acids requires two steps - making variants and testing them using the guidance in the specification (response pg 9-10).

This is not found persuasive because, given the lack of guidance in the specification, one would need to use trail and error experimentation to make the claimed nucleic acids. Further, given the higher similarity of SEQ ID NO:20 to mammalian toxins than insect toxins, one would be likely to make an mammalian toxin, which could not be sued to make the plants that would have use in the real world.

Conclusion

5. **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne R. Kubelik, whose telephone number is (571) 272-0801. The examiner can normally be reached Monday through Friday, 8:30 am - 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anne Marie Grunberg, can be reached at (571) 272-0975.

The central fax number for official correspondence is (571) 273-8300.

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Anne Kubelik, Ph.D.
September 14, 2007

ANNE KUBELIK, PH.D.
PRIMARY EXAMINER